Complete Summary

GUIDELINE TITLE

Hormone replacement therapy and venous thromboembolism.

BIBLIOGRAPHIC SOURCE(S)

Royal College of Obstetricians and Gynaecologists (RCOG). Hormone replacement therapy and venous thromboembolism. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2004 Jan. 9 p. (Guideline; no. 19). [48 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.

COMPLETE SUMMARY CONTENT

IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Venous thromboembolism associated with hormone replacement therapy

GUIDELINE CATEGORY

Counseling
Management
Prevention
Risk Assessment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To enable physicians to assess thrombotic risk in patients undergoing or starting hormone replacement therapy

TARGET POPULATION

Women undergoing or considering hormone replacement therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Counseling

1. Personal and family history of venous thromboembolism (VTE) or risk factors for VTE
2. Counselling of women starting or continuing hormone replacement therapy (HRT) concerning risk of VTE
3. Thrombophilia screening (for women with a personal or family history of VTE)
    - Activated partial thromboplastin time and prothrombin time
    - Antithrombin activity
    - Protein C activity
    - Total and free protein S antigen

- Modified activated protein C resistance (after predilution in factor V deficient plasma)
- Factor V Leiden (optional if modified APC resistance abnormal)
- Prothrombin 20210A variant
- Lupus anticoagulant and anticardiolipin antibodies (immunoglobulins G and M)

4. Routine haematology and biochemistry
    - Full blood count including platelet count
    - Urea and electrolytes, liver function tests and urinalysis for protein

Management

1. Avoidance of oral HRT in women with personal or family history of VTE
2. Use of transdermal HRT in women with personal or family history of VTE
3. Discontinuation of HRT in women who develop a VTE
4. Consultation with a clinician with expertise in thrombosis and thrombophilia
5. Anticoagulation therapy in women after VTE who continue to use HRT
6. Thromboprophylaxis prior to surgery in women using HRT

Universal screening of women for thrombophilic defects prior to or continuing the prescription of HRT was considered but not recommended.

MAJOR OUTCOMES CONSIDERED

Risk for and incidence of venous thromboembolism (VTE) associated with hormone replacement therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original articles for the evidence base for this guideline were obtained following a computer search for "hormone replacement" as a keyword and also in combination with "venous thrombosis" or "deep venous thrombosis" (DVT) or "pulmonary embolism" or "thrombophilia" applied to Medline (1966 to April week 1 2003), Embase (1980 to Week 15, 2003), Evidence-based Medicine Reviews, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness to the first quarter 2003.This was complemented by hand searching from individual references identified from these original articles.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

Ib: Evidence obtained from at least one randomised controlled trial

IIa: Evidence obtained from at least one well-designed controlled study without randomisation

IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study

III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The recommendations were graded according to the level of evidence upon which they were based. The grading scheme used was based on a scheme formulated by the Clinical Outcomes Group of the National Health Service (NHS) Executive.

Grade A - Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)

Grade B - Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendations (evidence levels IIa, IIb, III)

Grade C - Requires evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV)

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Following discussion in the Guidelines and Audit Committee, each green-top guideline is formally peer reviewed. At the same time the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) website for further peer discussion before final publication.

The names of author(s) and nominated peer reviewers are included in the original guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Levels of evidence (**Ia-IV**) and grading of recommendations (**A-C**) are defined at the end of the "Major Recommendations" field.

Women Starting or Continuing Hormone Replacement Therapy (HRT)

C - Women starting or continuing HRT should be counselled with regard to the perceived benefits and possible risks for their individual situations including consideration of alternative therapies.

C - Universal screening of women for thrombophilic defects prior to or continuing the prescription of HRT is inappropriate.

C - Prior to commencing HRT, a personal history and a family history assessing the presence of venous thromboembolism (VTE) in a first- or second-degree relative should be obtained.

C - HRT should be avoided in women with multiple pre-existing risk factors for VTE.

As VTE may be dependent upon multiple risk factors coming together, it is important to be aware of the presence of pre-existing thrombotic risk factors. In particular, the prescriber should specifically ask whether there is a previous personal history of VTE or a history of VTE in a first- or second-degree relative. If positive, thrombophilia testing (see Table below) may be considered. The presence of multiple pre-existing risk factors for VTE may suggest that HRT, itself a risk factor, might be best avoided. In particular, women with a previous VTE are at high risk of recurrence. However, it is important to review the overall situation for each individual. [Evidence level IV]

Table. Investigations for Potential Thrombophilia

Thrombophilia screen
• Activated partial thromboplastin time and prothrombin time • Antithrombin activity • Protein C activity • Total and free protein S antigen • Modified activated protein C resistance (after predilution in factor V deficient plasma) • Factor V Leiden (optional if modified APC resistance abnormal) • Prothrombin 20210A variant • Lupus anticoagulant and anticardiolipin antibodies (immunoglobulins G and M)
Routine haematology and biochemistry
• Full blood count including platelet count • Urea and electrolytes, liver function tests, and urinalysis for protein

Women with a Personal or Family History of VTE

C - Testing for thrombophilia should be discussed with and available for women with a personal or family history of VTE.

Testing for thrombophilia (as set out in the table above) may be helpful in women with a personal or family history of VTE. An attempt should be made to assess the severity of any previous event and whether or not it was objectively confirmed. The clinical diagnoses of deep vein thrombosis (DVT) and pulmonary thromboembolism are unreliable, and objective testing is required. However, in the past, objective testing was less available. A history of prolonged anticoagulant therapy would be compatible with a significant previous event.

A - It is recommended that, in women with a previous VTE, with or without an underlying heritable thrombophilia, oral HRT should usually be avoided in view of the relatively high risk of recurrent VTE.

Where the woman has had a previous VTE, with or without an underlying thrombophilia, oral HRT should usually be avoided in view of the relatively high risk of recurrence. However women must be considered as individuals. In each case, the woman's requirement for oestrogen replacement must be defined and the potential benefits for her weighed against the risks. [Evidence level Ib]

If it is considered that HRT is necessary for a particular woman, the risk of recurrence should be discussed carefully with her and she must be advised to report promptly if any symptoms compatible with VTE arise. In this situation, prophylactic anticoagulant therapy can be used while the woman is taking HRT. However, if anticoagulant thromboprophylaxis has to be used, the risk of haemorrhage must be considered in the risk-benefit analysis. On standard anticoagulant thromboprophylaxis, major haemorrhage occurs at a rate of around 1% per year of treatment and one-quarter of these bleeds are fatal. Transdermal therapy may be best in such a situation. Specialist advice from a clinician with expertise in thrombosis and thrombophilia should be sought. [Evidence level IV]

B - In women without a personal history of VTE but with an underlying thrombophilic trait that is identified through screening, HRT is not recommended in high-risk situations such as Type 1 antithrombin deficiency or with combinations of defects or additional risk factors for VTE and specialist advice should be sought.

Where there is no personal history of VTE but an underlying thrombophilic trait is identified through screening, because a first- or second-degree relative has a history of previous VTE (e.g., apparently spontaneous VTE, VTE at young age, VTE events in two or more family members), HRT should be avoided in high-risk situations such as type 1 antithrombin deficiency or combinations of defects and specialist advice should be sought. With other thrombophilic defects, there is insufficient evidence at present to indicate that HRT should be completely avoided, although evidence indicates around an eight-fold increase in risk of VTE. An assessment of other risk factors for VTE should be made. In the presence of multiple risk factors for VTE, HRT should be avoided. [Evidence level III]

If HRT is to be used, a clear discussion of the potential excess risk should occur with the woman and transdermal therapy may be best. Consideration should be given to "covering" oestrogen replacement with anticoagulant thromboprophylaxis taking into account the risk of haemorrhage. The risk of anticoagulant-related haemorrhage probably outweighs the risk of HRT-related venous thrombosis in women with a family history of VTE but no personal history of VTE, who have no identifiable thrombophilic defect or who have one of the defects usually associated with a lesser risk of VTE (heterozygosity for factor V Leiden or the prothrombin 20210A polymorphism). As this is a controversial and rapidly developing area, advice should be sought from clinicians with special expertise in thrombophilia. [Evidence level III]

C - In women over 50 years with a history of VTE within the previous year, a full clinical history and examination with appropriate investigations is warranted for underlying disease.

VTE may be precipitated by an underlying malignancy or connective tissue disease, so it is important to consider such a diagnosis in assessing women over 50 years of age with a recent pVTE. [Evidence level IV]

A - It is recommended that, when a woman who is on HRT develops a VTE, HRT should be discontinued.

C - It is recommended that, if a woman requires to continue on HRT after a VTE, long-term anticoagulation should be considered.

Risk of VTE in Users of Selective Oestrogen Receptor Modulators (SERMs)

B - SERMs should be considered to carry the same risk of thrombosis as oestrogen-containing HRT.

Women on HRT Undergoing Surgery

C - HRT should be considered a risk factor for VTE when assessing women preoperatively. However, HRT does not require to be routinely stopped prior to surgery provided that appropriate thromboprophylaxis, such as low-dose or low-molecular-weight heparin, with or without thromboembolic deterrent stockings, is used (Hoibraaten et al., 2000; Ettinger et al., 1999)

Definitions:

Grading of Recommendations

Grade A - Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)

Grade B - Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendations (evidence levels IIa, IIb, III)

Grade C - Requires evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV)

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

Ib: Evidence obtained from at least one randomised controlled trial

IIa: Evidence obtained from at least one well-designed controlled study without randomisation

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III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate treatment of women with hormone replacement therapy, and prevention of thromboembolism in patients at risk

POTENTIAL HARMS

Side effects associated with hormone replacement therapy, and anticoagulant thromboprophylaxis

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Clinical guidelines are "systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions." Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of Royal College of Obstetricians & Gynaecologists (RCOG) Green-top Guidelines*.

- These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Royal College of Obstetricians and Gynaecologists (RCOG). Hormone replacement therapy and venous thromboembolism. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2004 Jan. 9 p. (Guideline; no. 19). [48 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jan

GUIDELINE DEVELOPER(S)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

SOURCE(S) OF FUNDING

Royal College of Obstetricians and Gynaecologists

GUIDELINE COMMITTEE

Guidelines and Audit Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Professor Deirdre J Murphy, MRCOG (Chair); Lizzy Dijeh (Secretary); Ms Toni Belfield, Consumers' Representative; Professor P R Braude, FRCOG, Chairman, Scientific Advisory Committee; Mrs C Dhillon, Head of Clinical Governance and Standards Dept.; Dr Martin Dougherty, A. Director NCC-WCH; Miss L M M Duley, FRCOG, Chairman, Patient Information Subgroup; Mr Alan S Evans, FRCOG; Dr Mehmet R Gazvani, MRCOG; Dr Rhona G Hughes, FRCOG; Mr Anthony J Kelly MRCOG; Dr Gwyneth Lewis, FRCOG, Department of Health; Dr Mary A C Macintosh, MRCOG, CEMACH; Dr Tahir A Mahmood, FRCOG; Mrs Caroline E Overton, MRCOG, Reproductive medicine; Dr David Parkin, FRCOG; Oncology; Ms Wendy Riches, NICE; Mr Mark C Slack, MRCOG, Urogynaecology; Mr Stephen A Walkinshaw, FRCOG, Maternal and Fetal Medicine; Dr Eleni Mavrides, Trainees Representative

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Guideline authors are required to complete a "declaration of interests" form.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site.

Print copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Bookshop, 27 Sussex Place, Regent's Park, London NW1 4RG; Telephone: +44 020 7772 6276; Fax, +44 020 7772 5991; e-mail: bookshop@rcog.org.uk. A listing and order form are available from the RCOG Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Guidance for the development of RCOG green-top guidelines. Clinical Governance Advice No 1. 2000 Jan. Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site.
- Searching for evidence. 2001 Oct. Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on October 14, 2005. This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection.

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